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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte PETER A. CROOKS,
AIMEE K. BENCE, and DAVID R. WORTHEN

Appeal 2009-013078
Application 09/881,215
Technology Center 1600

Decided: February 19, 2010

Before ERIC GRIMES, LORA M. GREEN, and
JEFFREY N. FREDMAN, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method of treating epilepsy with agmatine. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

Statement of the Case

Background

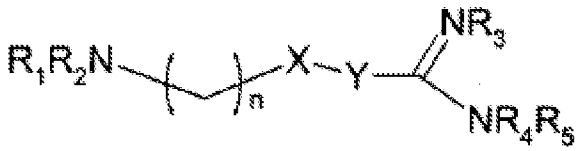
"Epilepsy is a general term describing brain disorders that are characterized by the occurrence of seizures" (Spec. 1, ll. 12-13). According to the Specification "[a]nti-epileptic drugs are available for treating epilepsies, but these agents have a number of shortcomings" (Spec. 2, ll. 21-22).

The Specification teaches the use of agmatine "in the prevention and/or treatment of all types of seizures and other electroconvulsive disorders" (Spec. 4, l. 27 to 5, l. 3).

The Claims

Claims 5, 7, 9, 11, and 13-20 are on appeal. Claim 5 is representative and reads as follows:

> 5. A method of treating, ameliorating, or preventing seizures associated with epilepsy in a subject in need thereof, the method comprising:
>
> administering a pharmaceutical composition comprising about 0.1 to about 500 mg of agmatine or an agmatine analog, or a pharmaceutically acceptable salt thereof per kilogram of the subject's weight to treat, reduce, or prevent seizures associated with epilepsy in the subject, wherein the agmatine analog has the following formula



> wherein n is 0 to about 10;
>
> R_1, R_2, R_3, R_4, and R_5, are each independently, or any combination thereof: hydrogen, hydroxy, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-8}

cycloalkyl, substituted or unsubstituted arylalkyl (comprising Ar-$(CH_2)_m$; where Ar is aromatic and m is 0 to about 10) substituted or unsubstituted C_{1-10} alkoxyl, substituted or unsubstituted C_{1-10} acyl, halogeno, amido, phenyl, thio, or amino; and

X and Y are each independently: O, NH, CH_2, CF_2, Se, C=O, C=N, or C=S, or X-Y together is HC=CH, C≡C, N=N, N=CH, CH=N, or a saturated or unsaturated ring.

The prior art

The Examiner relies on the following prior art references to show unpatentability:

Rajasekaran et al., *Effect of acute and repeated administration of nitric oxide (NO) precursor L-arginine, NO donor, sodium nitroprusside and NO synthase inhibitor, N (omega)-L arginine methyl ester on picrotoxin-induced seizure in rats*, 6TH INTERNET WORLD CONGRESS FOR BIOMEDICAL SCIENCE, poster 129 (2000).

Uzbay et al., *Effect of agmatine on ethanol withdrawal syndrome in rats*, 107 BEHAVIOURAL BRAIN RESEARCH, 153-159 (2000).

The Appellants rely on the following prior art reference :

Li et. al., *Agmatine is synthesized by a mitochondrial arginine decarboxylase in rat brain*, Annals New York Academy of Sciences, 763, pp. 325-329 (1995).

The issues

A. The Examiner rejected claims 5, 7, 9, 11, and 13-20 under 35 U.S.C. § 112, first paragraph "because the specification, while being enabling for treatment of seizure using agmatine, does not reasonably provide enablement for preventing seizure using agmatine" (Ans. 3-5).

B. The Examiner rejected claims 5, 7, 9, 11, and 13-20 under 35 U.S.C. § 103(a) as obvious over Uzbay and Rajasekaran (Ans. 5-7).

A. 35 U.S.C. § 112, first paragraph, enablement

The Examiner finds that "[s]ince compound structure and activity for . . . pharmaceutical use must be determined from case to case by painstaking experimental study, one of ordinary skill in the art would be burdened with undue experimentation to determine the preventative effect of agmatine on seizures" (Ans. 5).

Appellants argue that the "fact that different types of seizures are treated with different agents does not in and of itself indicate[ ] that a person having ordinary skill in the art would have to engage in experimentation that would be burdensome to practice the claimed subject matter" (App. Br. 6).

In view of these conflicting positions, we frame the enablement issue before us as follows:

Have Appellants demonstrated that the Examiner erred in finding that undue experimentation would have been required to prevent seizures associated with epilepsy by administering agmatine or an agmatine analog?

Breadth of Claims

1. Claim 5 encompasses a method of "preventing seizures associated with epilepsy" by "administering a pharmaceutical composition

comprising . . . agmatine or an agmatine analog, or a pharmaceutically acceptable salt thereof" (Claim 5).

Presence of Working Examples

2. The Specification teaches that the "Maximal Electroshock Seizure (MES) . . . is an experimental model for generalized tonic-clonic seizures that identifies compounds which prevent seizure spread. The MES model is highly reproducible and has a consistent endpoint" (Spec. 14, ll. 24-28).

3. The Specification teaches the "results of the MES test demonstrate that agmatine is effective in preventing seizure spread in the rat" (Spec. 15, ll. 18-19).

4. The Specification teaches that "[t]hese data indicate that the oral administration of agmatine (30 mg/kg) may have both acute (0-1 hours) and delayed (2-6 hours) inhibitory effects on MES-induced seizure spread" (Spec. 15, ll. 26-29).

5. The Specification teaches that "[i]n rats and mice, agmatine was demonstrated to be devoid of any neurological toxicity" (Spec. 17, ll. 3-4).

Amount of Direction or Guidance Presented

6. The Specification teaches that "agmatine, an agmatine analog, or a pharmaceutically acceptable salt, complex or cogener thereof is formulated into a pharmaceutical preparation comprising the active agent and a pharmaceutically acceptable carrier" (Spec. 9, ll. 1-4).

7. The Specification teaches that "[i]t has been discovered that the inventive compositions are useful in the prevention, palliation and/or

treatment of seizures, conduction disturbances, and electroconvulsive disorders of all types" (Spec. 9, ll. 4-6).

8. The Specification teaches that "[p]revention of the condition or disorder is manifested by delaying the onset of the symptoms of the conditions or disorder" (Spec. 14, ll. 7-8).

State of the Prior Art and Unpredictability of the Art

9. The Examiner finds that the "prior art does not recognize that the prevention of seizures is done easily. According to Lance[1] . . . different types of seizures are treated with different agents. There are no teachings directed to prevention of seizures" (Ans. 4).

10. The Specification teaches that "[a]nti-epileptic drugs are available for treating epilepsies, but these agents have a number of shortcomings" (Spec. 2, ll. 21-22).

11. The Specification teaches that "[e]ven while being treated with one or a combination of the anti-epileptic drugs currently in clinical use, 30% of epileptic patients still experience seizures," which indicates that current drugs "prevent" 70% of patients from experiencing seizures (Spec. 2, ll. 26-28).

12. The Examiner finds, without evidence cited, that the "unpredictability of pharmaceutical and chemical art is high" (Ans. 4).

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[1] The Examiner has not included Lance in the "Evidence Relied Upon" section of the Answer, nor has the Examiner provided a copy of Lance in the record for review by Appellants or us.

Quantity of Experimentation

13. The Examiner finds that "compound structure and activity for such pharmaceutical use must be determined from case to case by painstaking experimental study" (Ans. 5).

Skill in the Art

14. The Examiner finds that the "relative skill of those in the art is high" (Ans. 4).

Principles of Law

> When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application.

In re Wright, 999 F.2d 1557, 1561-62 (Fed. Cir. 1993). "[T]he question of undue experimentation is a matter of degree. The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.'" *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

> Factors to be considered in determining whether a disclosure would require undue experimentation … include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

Analysis

The Examiner bears the burden of providing an explanation as to why the claims are not adequately enabled by the Specification. *In re Wright*, 999 F.2d at 1561-1562. In this case, the Examiner's position appears to be that the Specification is not enabled for preventing epileptic seizures by administration of agmatine because "one of ordinary skill in the art would be burdened with undue experimentation to determine the preventative effect of agmatine on seizures" (Ans. 5).

In analyzing the *Wands* factors, based upon the evidence presented by the Examiner, all of the factors are clearly either neutral or support the enablement position of Appellants (FF 1-14). The claims are narrowly drawn to treating and preventing seizures associated with epilepsy by administering agmatine or an agmatine analog (FF 1; Claim 5). The Specification has an *in vivo* working example which shows that "agmatine is effective in preventing seizure spread in the rat" (Spec. 15, ll. 18-19; FF 3). The working example also demonstrates that "oral administration of agmatine (30 mg/kg) may have both acute (0-1 hours) and delayed (2-6 hours) inhibitory effects on MES-induced seizure spread" (Spec. 15, ll. 26-29; FF 4).

The prior art clearly recognizes that drugs exist which are capable of at least partially preventing seizures caused by some forms of epilepsy (FF 10-11). There is no evidence that a large quantity of experimentation would be required (FF 13) nor is there specific evidence that the use of agmatine in "preventing" seizures in epilepsy is unpredictable (FF 12).

With regard to skill level in the art, the Examiner acknowledges that the skill level is "high" (FF 14). While Appellants are correct that no evidence is adduced to support this determination, the Examiner's finding of a "high" skill level supports enablement of the claims, since the skilled artisan requires less disclosure in the Specification.

While we cannot directly address the Lance reference, since it was not properly cited by the Examiner nor provided in the working file, a generic reference teaching that different seizures are treated with different agents would not persuasively overcome the *Wands* factors supporting enablement.

We are not persuaded by the Examiner's argument, regarding the Specification's data, that "[s]uch data inhibit the occurrence of seizure in a number of animals for a limited amount of time" (Ans. 7). This is evidence supporting enablement which is not rebutted by the Examiner. The Examiner has not provided the required evidence or scientific reasoning to show that one of ordinary skill in the art would find that preventing seizures associated with epilepsy by administration of agmatine or agmatine analogs would have required "undue experimentation". The Examiner's mere assertions to that effect are not sufficient for establishing a prima facie case of lack of enablement.

Conclusion of Law

Appellants have demonstrated that the Examiner erred in finding that undue experimentation would have been required to prevent seizures associated with epilepsy by administering agmatine or an agmatine analog.

B. 35 U.S.C. § 103(a) over Uzbay and Rajasekaran

The Examiner finds that "Uzbay et al. teach the use of agmatine (40 mg) for the treatment of audiogenic seizure due to ethanol withdrawal" (Ans. 6). The Examiner finds that "Rajasekaran et al. teach the anticonvulsant activity of agmatine used in the treatment of seizure caused by epilepsy" (Ans. 6). The Examiner concludes that "[i]t would have been obvious to a person skilled in the art to modify Uzbay's teachings in view of Rajasekaran to treat seizure caused not only by ethanol withdrawal, but also seizure due to epilepsy" (Ans. 6).

Appellants argue that the "teachings of Uzbay *et al.* are clearly limited to and relevant only to ethanol withdrawal syndrome associated" (App. Br. 7). Appellants argue that the "data in Uzbay et al. establish a failed attempt to treat seizures with agamatine, i.e., these studies agmatine was not effective in treating seizures related to alcohol abuse" (App. Br. 8). Appellants argue that "Rajasekaran et al. merely suggest that the anticonvulsant activity of L-arg may be effected through agmatine, but they offer no evidence to that effect" (App. Br. 9). Appellants argue that "Rajasekaran et al. do not provide any data concerning agmatine to show that it is effective for treating, ameliorating or preventing seizures associated with epilepsy as required by claims 5 and 13" (App. Br. 10).

In view of these conflicting positions, we frame the obviousness issue before us as follows:

Have Appellants demonstrated that the Examiner erred in concluding that the combination of Uzbay and Rajasekaran renders obvious the treatment or prevention of epileptic seizures with agmatine?

Findings of Fact

15. Uzbay teaches that "agmatine, an arginine metabolite, has some inhibitory effects on the withdrawal syndrome in ethanol-dependent rats" (Uzbay 156, col. 2).

16. Uzbay teaches that "[t]hese inhibitory effects of agmatine on ethanol withdrawal syndrome may be explain[ed] by three mechanisms" (Uzbay 156, col. 2).

17. The Examiner notes that Uzbay "differs from the claimed invention in treating seizure caused by epilepsy" (Ans. 6), recognizing that Uzbay is silent regarding epilepsy.

18. Rajasekaran teaches that "NO [nitric oxide] has been implicated in the pathogenesis of neurodegenerative disorders including Alzheimer's disease, parkinsomism, Huntington's disease and epilepsy" (Rajasekaran, Introduction).

19. Rajasekaran teaches that "NO could be an important pathogenic component in the mechanisms that regulate seizure induction, propogation [sic] and progression. The role of NO in epilepsy remains debatable" (Rajasekaran, Introduction).

20. Rajasekaran teaches that the "results of the present study provide an evidence for the anticonvulsant activity of L-arginine as well as a proconvulsant role for NO" (Rajasekaran, Discussion).

21. Rajasekaran teaches that the "anticonvulsant activity of L-arg may be direct . . . or a product of its metabolism such as agmatine (Li et al.,

1995) or to the possible accumulation of L-arg per se" (Rajasekaran, Discussion).

22. Rajasekaran teaches that "we conclude that NO facilitates seizures and that an inhibition of NO may prevent seizures. Further, the results indicate that the anticonvulsant action of L-arginine may not be essentially . . . mediated by the NOS [nitric oxide synthase] pathway" (Rajasekaran, Conclusions).

23. Li teaches that "agmatine (decarboxylated arginine) is contained in bovine brain" (Li 325, abstract).

24. Li discloses that "rat brain expresses an enzyme that can synthesize agmatine and CO_2 from L-arginine" (Li 328).

Principles of Law

"[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l v. Teleflex Inc.*, 550 U.S. 398, 418 (2007).

The Examiner has the initial burden of establishing a prima facie case obviousness under 35 U.S.C. § 103. *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992) ("[T]he examiner bears the initial burden, on review of the prior art or on any other ground, of presenting a *prima facie* case of unpatentability.").

In *O'Farrell*, the court held that a conclusion of obviousness was appropriate where the prior art "contained detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to

practice the claimed invention, and evidence suggesting that it would be successful." *In re O'Farrell*, 853 F.2d 894, 902 (Fed.Cir.1988).

Analysis

Uzbay teaches that agmatine has some efficacy in treating ethanol withdrawal in rats, but provides no teaching or suggestion regarding the application of agmatine to epilepsy as required by Claim 5 (FF 15-17). Rajasekaran notes that nitric oxide has been linked to diseases including epilepsy (FF 18), but notes that this linkage remains debatable (FF 19). Rajasekaran teaches that L-arginine functions as an anticonvulsant (FF 20), but does not determine the mechanism and merely suggests that one possible modality is by the metabolic product agmatine (FF 21). Rajasekaran demonstrates that the pathway of action of L-arginine is unpredictable and may not be through NOS (FF 22). Further, Rajasekaran cites Li simply to show that agmatine is a metabolic product of L-arginine, not to show a relationship between agmatine or L-arginine and seizure or epilepsy (FF 23-24).

The Examiner finds that the "mere fact that Rajasekaran et al. teach the anticonvulsant activity of arginine may be due to its metabolite agmatine, makes the use of agmatine as an anti-seizure drug obvious to a person skilled in the art" (Ans. 8)

Appellants argue that "Rajasekaran et al. do not provide any data concerning agmatine to show that it is effective for treating, ameliorating or preventing seizures associated with epilepsy as required by claims 5 and 13" (App. Br. 10).

We find that Appellants have the better position. While Rajasekaran indirectly connects agmatine and seizures (FF 18-22), on this particularized set of facts, we do not agree with the Examiner that it was obvious that agamatine would have predictably functioned to treat epilepsy.

We conclude that the application of agmatine to the treatment of epilepsy was not predictable or simply the result of routine experimentation. While *O'Farrell* states that "[o]bviousness does not require absolute predictability of success", *O'Farrell* identifies

> two kinds of error. In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. . . . In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

In re O'Farrell, 853 F.2d 894, 903 (Fed.Cir.1988). The instant situation fits *O'Farrell's* second kind of error, since the prior art of Rajasekaran at best provides general guidance regarding metabolites of L-arginine that might function as anticonvulsants. While inhibitors of NO might represent a promising field of experimentation, the prior art cited by Rajasekaran recognizes that the role of NO in epilepsy is debatable (FF 19). Rajasekaran itself recognizes that the pathway by which L-arginine operates is unclear (FF 22). With regard to even general guidance, neither Rajasekaran or Uzbay identify or suggest agmatine as a treatment for epilepsy.

Further, while *KSR* recognizes that "the fact that a combination was obvious to try might show that it was obvious under § 103," *KSR* teaches that this applies "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions" and it is in that situation that "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp" *KSR*, 550 U.S. at 421. The Examiner makes none of the requisite findings to demonstrate that the use of agmatine as an anticonvulsant is predictable, that there are a finite number of solutions, or that the use of agmatine for treatment of epilepsy was even "obvious to try."

Conclusion of Law

Appellants have demonstrated that the Examiner erred in concluding that the combination of Uzbay and Rajasekaran renders obvious the treatment or prevention of epileptic seizures with agmatine.

SUMMARY

In summary, we reverse the rejections of claims 5, 7, 9, 11, and 13-20 under 35 U.S.C. § 112, first paragraph.

We reverse the rejection of claims 5, 7, 9, 11, and 13-20 under 35 U.S.C. § 103(a) as obvious over Uzbay and Rajasekaran.

REVERSED

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